REMARKS

Claim 21 has been amended in response to the objection of being an improper multiple dependent claim so that claim 21 is now dependent on claim1. For this reason, it is req1uested that this ground of rejection be withdrawn.

The Examiner has rejected claims 1-3, 6-11, 14-27, 29-33, 36-41 44-46, and 48-60 under 35 U.S.C.§103(a) as unpatentable over Santus et al. (U.S.P.N. 5,472,704, herein Santus).

Rcconsideration is requested.

Claim 1 and all of the independent claims have been amended to recite the ratio of the drug to polymer and micro-matrix particles to the coating. These ratios were disclosed in the specification at page 12, lines 21-33 and in original claims 6 and 7. These ratios point out a low level of coatings which allow for the reduction in size of a dosage form with the subsequent advantage of easier swallowing and improved patient compliance with the dosing of critical medications which is achieved without loss of the controlled release feature of the invention. The ratios have been added in response to the Examiner's comment that the size was not recited in the claim. The inclusion in all claims of the ratios

of the hydrophobic agent now limits the amounts that can be used in relation to the active ingredient and as a consequence limits the size of the dosage form which will not have more than a therapeutic dose of the active ingredient.

It is not practical to recite a size for a dosage form but the ratio of the hydrophobic agent does provide a limitation on size when considering the absence of a the teaching of this ratio from the cited references. This amendment adds to the independent claims an unobvious feature that is not taught in the prior art. In addition the claimed ratio is recited in combination with the novel dual retard feature that was previously recited in all of the independent claims. The Applicant wishes to emphasize that the claims before the Examiner are limited to dosage forms having a highly soluble active ingredient. These types of active ingredients cause special problems when they are formulated into a modified release dosage formulation.

Many of the prior art modified delivery systems have utilized matrix dosage forms provide useful levels of controlled release for the delivery of sparingly soluble drugs. However, and particularly for highly soluble drugs, such a matrix does not provide adequate control over the release rate. Instead, the release profile that is seen in those formulations approximates first-order kinetics and problems with dose dumping or burst release prevent the use of such formulation for modified release compositions. A further difficulty arise with many modified release dosage forms that contain comparatively large amounts of highly soluble active ingredients is the large dose size that is required to accommodate large amounts of excipients in order to achieve appropriate controlled release profiles.. The present invention provides reduced dosage form sizes as a result of the dual retard system that uses the recited ratios of active to hydrophobic release agent and micro-matrix particles to hydrophobic release coating. As such, the amended claims point out non-obviousness subject matter by reciting a technique which can effectively control the release of the highly soluble active ingredient as well as having a small size.

Santus discloses various methods to prepare controlled release microunits (Column 4,

lines: 35 - 42). Those controlled release microunits are:.

1. Reservoir units
2. Matrix units
3. Osmotic units
4. Biodegradable units

While the Examiner has noted that the interpretation of Santus is not limited to the preferred embodiment, such an argument points out the needle-in-the-haystack problem that a skilled artisan encounters when a prior art reference is considered. With regard to novelty, the existence of multiple embodiments is not relevant to what the reference actually discloses because if it exists in a reference, novelty is destroyed. When it comes to a determination of what is made obvious by a reference, the existence of multiple embodiments that are all different from what the inventor ultimately determines is a workable solution to a problem, raises a practical question as to how does Santus make obvious the claimed invention. Would a person skilled in art, who is assigned the task of designing a compact dosage form having reduced size, be directed to carry out exhaustive experimentation with all the controlled release system as disclosed in Santus when Santus gives no guidance as to how to make a controlled release system which is a dual retard system

In any event, Santus teaches that, based on the amount of a highly soluble active ingredient, the choice of matrix units is more complex than that of reservoir unit (Column 4, lines 60-61) and hence it would invite lot of experimentation without a guarantee of success. Apart from this disclosure by Santus, the choice of controlled release microunits from the above mentioned method is critical for person having ordinary skill in the art. The drug release from these microunits are also dependent on physiochemical and pharmacokinetic properties of the active ingredient and it does not follow that a person skilled in the art could manufacture a modified release dosage form based on high solubility active ingredient and effectively control the release of the highly soluble active ingredient as well as having a small size, even if exhaustive experimentation was undertaken.

Applicant further emphasizes that many of the prior art modified delivery systems utilizing matrix dosage forms provide useful levels of control to the delivery of sparingly soluble drugs. However, and particularly for highly soluble drugs, such a matrix does not provide adequate control over the release rate. Although, Santus discusses use of hydrophobic polymers for controlling release of highly soluble drugs but gives no guidance as to how to reduce the size of a dosage form by selection of a dual retard system and the use of the specified ratios of material in amended claims 1, 30, 31 and 60.

The claimed dual retard technique, as pointed out in the amended claims avoids the burst effect and effectively control the release rate of high solubility active ingredients for prolonged periods using smaller quantities of release controlling agents. This has been demonstrated in figures 2, 3, and 4 of the instant application. Furthermore, figures 2-4 clearly show that when release rates of formulations containing the same quantity of hydrophobic release controlling agents were manufactured by dual retard techniques and with simple matrix technique, as in Santus, the formulations with dual retard technique significantly reduced the burst effect and controlled the release rate of a high solubility active ingredient for a prolonged period.

Therefore, Applicant respectfully submits that the amended claims are not obvious in light of Santus.

The Examiner has rejected claims 4, 5, 12, 13, 28, 34, 35, 42, 43 and 47 under 35 U.S.C. § 103(a) as being obvious in view of Santus, further view of Akiyama et al (US Patent 5,399,357) (Aikyama)..

Reconsideration is requested.

Santus has been distinguished from the claimed invention above. Akiyama discloses a controlled release matrix composition using melt granulation technique. The only criteria for selecting an active ingredient for the Akiyama sustained release composition, is the melting point of the compound. There is no mention of the use of highly soluble drugs in the Akiyama melt granulation procedure. Therefore, one skilled in the art would not be motivated

by Santus to use any procedure from Akiyama for the making of a dosage formulation of a highly soluble drug. Moreover, as disclosed in all the Akiyama Examples (1-30), the large amounts of fatty acid ester of polyglycerol (release controlling agent) must be used to obtain the desired release profile. Thus even if person skilled in art uses the teaching of Akiyama, much like Santus, this will ultimately increase the size of the formulation because the references are silent as to the need to limit the ratio of the hydrophobic release agent, as specified in the amended claims of the present application.

The amended claims of the present application point out modified release formulations which are entirely different from the subject matter disclosed by Akiyama when that patent is considered with or without Santus.. The amended claims recite high solubility active ingredient and one or more hydrophobic release controlling agents that are mixed and granulated by adding a solvent, whereas according to Akiyama matrix preparation is manufactured by melting fatty acid ester of polyglycerol and adding the active ingredient and other ingredients into the molten mass, which is then converted into granules by spray cooling (Col 6, lines 30 - 65).

The combined prior art reference teach the use of large amounts of excipients and polymers, which will lead to unacceptably large dosage form, particularly for high solubility active ingredient such as metformin. Finally, both references themselves teach cumbersome techniques such as slugging and melt granulation without any suggestion of the use of a dual retard technique, as pointed out in each of the amended independent claims. Furthermore, any combination of Akiyama and Santus would require undue experimentation without any direction that would necessarily lead to the results described in the present specification. At best, any resulting combination would result in a large dosage form containing a fatty acid ester. More importantly, the dual retard technique of the amended claims can not be found anywhere in the cited prior art references. Therefore, Akiyama, alone or combined with the teaching of Santus, fails to teach a person skilled in the art the dual retard technique for high

solubility active ingredient as recited in the amended claims. For these reason, it is requested that this ground of rejection be withdrawn.

In response to the provisional double patenting rejections, it is premature to require the submission of terminal disclaimers. Upon the indication of allowable subject matter, a terminal disclaimer will be filed.

Favorable consideration and early allowance are therefore respectfully requested and earnestly solicited.

Respectfully Submitted,

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